REVIEW

Prospects for harnessing biocide resistance for bioremediation and detoxification

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Prokaryotes in natural environments respond rapidly to high concentrations of chemicals and physical stresses. Exposure to anthropogenic toxic substances—such as oil, chlorinated solvents, or antibiotics—favors the evolution of resistant phenotypes, some of which can use contaminants as an exclusive carbon source or as electron donors and acceptors. Microorganisms similarly adapt to extreme pH, metal, or osmotic stress. The metabolic plasticity of prokaryotes can thus be harnessed for bioremediation and can be exploited in a variety of ways, ranging from stimulated natural attenuation to bioaugmentation and from wastewater treatment to habitat restoration.

Microorganisms in pristine ecosystems as well as those in anthropogenically disturbed habitats are constantly challenged by combinations of chemicals and physical stresses. Natural habitats can experience combinations of conditions from high salinity and osmolarity, desiccation, ultraviolet radiation, high pressure, or extremes of pH or temperature (*1*). Industrial, agricultural, and domestic activities lead to the release of organic and inorganic compounds toxic to a wide range of organisms in the environment. Microbes exposed to such conditions can rapidly develop physiological and/or genetic adaptations to resist environmental constraints. Harnessing the metabolic capacities of prokaryotes and their adaptive potential is of interest for a broad range of applications for environmental clean-up as well as for treatment of domestic and industrial waste.

Microbial tolerance and resistance mechanisms

The mechanisms that enable bacteria to survive typical environmental stressors, such as toxic concentrations of organic pollutants and changes in temperature or osmolarity, are well understood (*2*–*4*). Preventing damage to the cell envelope and cellular membranes are pivotal for prokaryote survival (*5*). Hence, one of the first responses to toxic assault is membrane repair to reestablish membrane fluidity and rigidity. In Gram-negative bacteria, this occurs with the insertion of saturated and *trans*-configurated unsaturated fatty acids, whereas in Gram-positive bacteria, *iso*-branched fatty acids are inserted (*6*). Cell-surface properties can also be modified during exposure to stressors by the release of outer-membrane vesicles, which increase surface hydrophobicity. This phenomenon can stimulate biofilm formation, making bacteria yet more tolerant to environmental stressors (*7*). Bacteria can also change their morphology in the presence of toxic concentrations of organic pollutants, increasing their overall size and decreasing surface-to-volume ratio (*5*).

Many bacteria respond to stresses by inducing synthesis of specific membrane efflux pumps. This response is well understood in bacteria capable of withstanding high concentrations of organic solvents such as benzene, toluene, ethylbenzene, and xylene (BTEX). BTEX are excreted from membranes by energy-driven protein pumps belonging to the root nodulation (RND) family of membrane proteins. RND proteins are known in other bacteria to transport antibiotics and contribute to multidrug resistance (*3*). Cross-protection to different stresses is common. For example, bacterial cells that adapt to a given solvent also show increased tolerance to other solvents, heavy metals, antibiotics, and several forms of physical-chemical stress. Because bacterial adaptive physiological responses are inducible, it is therefore possible to pre-adapt the cells for potential applications at contaminated sites (*5*).

Role of environments in tolerance and resistance selection

Although any environment ultimately selects for the survival and proliferation of specific microbial genotypes, extreme and polluted environments showcase the power of such selective forces. Polluted environments are frequently characterized by high concentrations of toxic substances that can appear in sudden, infrequent, but ephemeral bursts such as oil spills (*8*), but equally, chronic pollution can arise from long-term input of pollutants (*9*). An influx of high concentrations of toxic compounds can lead to dramatic shifts in microbial community composition and diversity (Fig. 1, top) (*10*). Consequently, carbon and nutrients in the system that are no longer used by sensitive phenotypes can be used for growth by resistant phenotypes (Fig. 1, top) (*11*). Additionally, polluting compounds can become an exclusive source of assimilable nutrients or electron donors or acceptors for resistant microorganisms (Fig. 1, bottom) (*11*). For example, oil-degrading bacteria occur at typically low abundances in marine environments but respond with astonishingly rapid blooms during oil spills (*12*). Even for synthetic chemicals considered to be xenobiotic—such as chlorinated solvents, pesticides, and the plastic poly(ethylene terephthalate)—release into the environment, and long-term pollution selects for the appearance and proliferation of mutants with naturally recombined metabolic pathways, which profit from the exclusivity of the toxic compound for growth (*13*–*15*). Natural recombination is largely the result of abundant horizontal gene flow in prokaryote communities. Diverse mechanisms have been implicated in gene flow, such as plasmid conjugation, natural transformation, and integrative and conjugative or transposable elements (*11*). Extreme toxicity resistance as a result of RND-type efflux mechanisms may thus be a prerequisite for further adaptation by keeping the intracellular concentration of the toxicant low enough to permit its metabolism (*16*).

As worldwide environmental concerns shift from high contamination loads of legacy chemicals—such as oil, polycyclic aromatic hydrocarbons, and polychlorinated biphenyls—toward low concentrations of biologically very active molecules—including antibiotics, other pharmaceuticals, and ingredients of household and consumer care products—the question is what types of microbial resistance will be selected by low and chronic concentrations of these chemicals. Although low concentrations of chemicals can be toxic to some lineages and may result in selection of resistant phenotypes, as the widespread emergence of antibiotic resistances attests, the distinct proliferation of "compound-degrader" phenotypes may be more difficult to discern. Conceivably, micropollutant degraders might have more advantage in oligotrophic environments (*17*), where available nutrients are scarce and the ability to metabolize micropollutants may be particularly competitive.

Concepts for harnessing toxicant-tolerant or -resistant bacteria

An important outcome of adaptation and selection in contaminated environments is that sites chronically polluted with organic compounds naturally restore over time and diminish the pollution load (*18*). Such natural attenuation and restoration processes may, however, take decades (*19*). Nevertheless, they require little technical intervention or cost. The spontaneous adaptation and selection that has led to the appearance of (naturally recombinant) bacteria capable of resisting or degrading contaminants has since long attracted interest for potential applications

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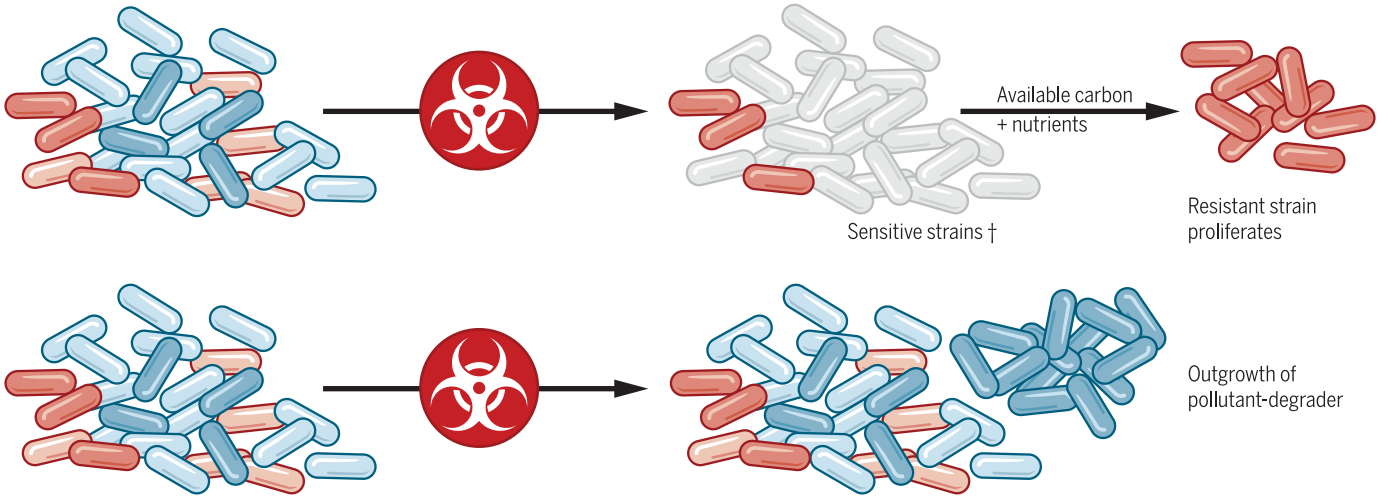

Fig. 1. Environmental selection of adaptive phenotypes to toxic compound stresses. (**Top**) Exposure of a diverse bacterial community to toxic concentrations of chemicals inhibits or kills sensitive individuals. Resistant organisms profit from the availability of unused carbon and nutrients in the system to proliferate. (**Bottom**) Toxic organic compounds themselves can be used as an exclusive growth substrate for low numbers of preexisting specialist bacteria in the community or for newly arising mutants. These lineages will proliferate by consuming the toxic compound, potentially leading to the spontaneous natural attenuation of a contaminated site. Specialist degrader bacteria may additionally profit from toxicity-resistance mechanisms.

elsewhere. The enrichment or isolation of promising pollutant-degrading bacteria, growth under laboratory conditions, and formulation for use in similar conditions and context—a process called bioaugmentation—could potentially shorten the long on-site adaptation process and accelerate remediation.

Bioaugmentation has been successfully applied at sites contaminated with organohalogen compounds. Organohalide-respiring bacteria (OHRB) such as *Dehalococcoides mccartyi*, *Dehalogenimonas* spp., and *Dehalobacter* spp. use chlorinated solvents and/or pesticides as their sole terminal electron acceptors for growth (*20*). Organohalide respiration is probably evolutionarily ancient (*21*), but traces of recent or even ongoing genetic adaptation are detectable in the genomes of these species. Precultured stocks of microbial consortia containing OHRB have been successfully applied so as to improve bioremediation of sites contaminated with chlorinated solvents such as tetrachloroethene (Fig. 2) (*20*, *22*). OHRB augmentation has been shown to be essential for on-site chlorinated solvent bioremediation because stimulation of the autochthonous OHRB frequently leads to accumulation of a more toxic transformation product, vinyl chloride (*23*).

Widespread pollution with hexachlorocyclohexanes (HCHs) arose around the world during production of the currently largely banned pesticide, the γ-HCH isomer lindane. Bacteria adapted to using HCHs as their sole carbon and energy sources have been discovered at HCH-contaminated sites (*24*) as a result of natural recruitment and recombination of existing genes and subsequent mutations. Such bacteria have been isolated, cultured in larger quantities, specifically formulated, and successfully used in the bioaugmentation of HCH-contaminated areas (*25*).

ADAPTED BY K. KHOLOSKI

Oil bioremediation

Crude oil is toxic to metazoan life yet is a supply of extremely energy-rich carbon sources for hydrocarbonoclastic bacteria. Hydrocarbonoclastic bacteria are ubiquitous and evolutionarily old lineages that have adapted to oil components released at natural oil seeps (*26*, *27*). Typically, their population size in the absence of oil spills is very small, but they bloom during oil contamination. For example, *Oceanospirillales* spp. can compose 90% of the local marine bacterial community after oil spillage (*27*). Two well-known species, *Alcanivorax borkumensis* and *Oleispira antarctica*, have evolved several adaptive strategies to optimize access to their poorly water-soluble aliphatic hydrocarbon substrates (*27*, *28*). These include an increase in cell surface hydrophobicity that is thought to favor partitioning of substrates into the cell envelope, as well as production of biosurfactants to increase the ambient solubility of the aliphatic hydrocarbons. Interestingly, *A. borkumensis* is also able to directly incorporate fatty acids, resulting from oxidation of aliphatic hydrocarbons, into its cell membrane (*28*).

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Although bioaugmentation of oil spills is often revisited, the application of large quantities of precultured marine hydrocarbonoclastic bacteria has not been very successful. A more effective measure for major spills seems to be through stimulation of the growth and activity of indigenous hydrocarbonoclastic bacteria with the application of lipophilic nitrogen-phosphorous–rich fertilizers, both in the open sea as well as on rocks and beaches contaminated with crude oil (*29*).

Oil spills in arid terrestrial environments are accompanied by the simultaneous occurrence of high pH, high salinity, and high loads of toxic organic compounds. In general, adaptation to osmotic stress under high salinity and pH requires increased intracellular salt concentration or accumulation of organic osmotic solutes (*30*). At elevated salinity, the microbial cell surface tends to become more hydrophilic, which will further limit physiological activity on hydrophobic hydrocarbons. High salt concentrations are also characterized by reduced dissolved oxygen, but some organisms can metabolize oil under these conditions, although the mechanisms are not well understood. Successful large-scale bioaugmentation has been implemented in a water pit (3600 m^3) heavily polluted with crude oil in northern Oman, where the addition of halophilic cultures reduced hydrocarbon concentrations from 10 to 40% (w/w) to below 1% (w/w) within a year (Fig. 3) (*31*).

Resistance to low pH and high concentrations of heavy metals

Metal extraction and metal leachate decontamination offers contrasting examples of microbial resistance and its potential use for bioremediation.

Fig. 2. Bioaugmentation with OHRB. (**Left**) Injection of microbial cultures containing OHRB in an injection well or (**Right**) direct push injection without the use of wells in aquifers contaminated with chlorinated solvents. [Reprinted by permission from Springer Nature, (*22*).]

Bioextraction and recovery of valuable metals from sulfidic ores (biohydrometallurgy) depends on the activity of sulfur- and iron-oxidizing prokaryotes to solubilize the mineral pyrite (FeS_2) to H_2SO_4 and Fe^{3+}, during which protons and other metals trapped within the pyrite matrix are released. Biohydrometallurgic suspensions have extreme physicochemical characteristics, sometimes with negative pH values, and metal and sulfate concentrations between 10 and 100 g liter^{-1} (*32*).

Consortia of acidophilic prokaryotes used for biohydrometallurgy, mainly belonging to the genera *Acidithiobacillus* and *Leptospirillum*, are typically derived from natural acid rock drainage environments, such as the Tinto river in Spain, or from spontaneous enrichments derived from mine drainage. These acidophiles can grow at extremely low pH and high metal concentrations. Although growth at low pH has some advantages for cellular energy conservation because it builds a spontaneous pH gradient for the proton motive force across the cytoplasmic membrane, the protons still have to be neutralized within the cytoplasm. Some extreme acidophiles prevent ingress of protons by importing K^+ ions, which inverts the membrane potential (positive inside). They can also have highly impermeable membranes owing to the presence of tetraether lipids and specific membrane transporters, such as antiporters, symporters, H^+–adenosine triphosphatases (ATPases), or metal-transporting P-type ATPases, which remove excess protons and metal ions from the cytoplasm. Additionally, specific chaperones have been reported in acidophilic bacteria that stabilize DNA and proteins, which would otherwise be damaged by the low pH (*33*).

Metal leachates from mines are highly problematic because of their low pH, high sulfate, and high dissolved metal content. Sulfate-reducing bacteria (SRB) release sulfide, which will increase the pH and will react with the dissolved metal ions to precipitate in the form of poorly soluble metal sulfides. Stimulation of sulfidogenic activity has been tested in pilot-scale treatment of metal leachate from the zinc smelter Nyrstar in the Netherlands, and also for leachates from the gold mine Pueblo Viejo in the Dominican Republic. Both applications, however, required prior neutralization of the leachates before biological treatment. Nevertheless, acid- and metallotolerant SRB, such as *Desulfosporosinus acididurans* (*34*), have been isolated from low-pH environments and successfully deployed for initial biological leachate neutralization and subsequent metal detoxification in laboratory-scale reactors (*35*). The prior growth of acidophilic SRB in pH-controlled reactors may further improve the biological recovery of precipitated metallic sulphides and allow potential reuse in industrial processes (*36*).

Resistance to antibiotics and nonantibiotic biocides

Application of antibiotics and nonantibiotic biocides has increased dramatically in recent decades and has resulted in widespread selection of resistant or tolerant mutants. Resistance to antibiotics by the selection of RND efflux pump mechanisms can provide cross-resistance to a wide range of other adverse conditions and compounds. Hence, antibiotic resistance also frequently co-occurs with resistance to biocides and heavy metals. This results from the colocalization and/or comigration of genes conferring multiple resistance mechanisms (*37*, *38*). Antibiotic resistance genes occur in microbes in natural environments without obvious anthropogenic exposure to antibiotics. This indicates that they confer additional biological advantages (*39*), such as resistance to other environmental stressors or to interspecies competition strategies, and metabolism of toxic compounds structurally similar to antibiotics. Several previously unknown dioxygenases have been retrieved from soil metagenomic libraries screened for resistance against β-lactam antibiotics (*40*). These enzymes were also shown to transform other aromatic compounds (*40*). Some microbes can use these antibiotics as substrates for growth, although the mechanistic basis for this antibiotic subsistence has not been identified unequivocally (*41*).

Nonantibiotic biocides can also select for proliferation of resistant microorganisms capable of their biotransformation, as has been shown for a river sediment microbial community degrading benzalkonium chlorides (*42*). Strains of *Pseudomonas putida* and *Alcaligenes xylosoxidans*—which are capable of resisting high levels of the polychlorinated antimicrobial triclosan and using it as a sole carbon source—have been isolated from soil (*43*). Biocide resistance could potentially be put to good use—for instance, for biocides removal from the filters of drinking water treatment plants (DWTPs). However, success has been limited so far. Augmentation of *Aminobacter* sp. MSH1 to sand filters in recent pilot-scale studies of DWTPs only temporarily increased 2,6-dichlorobenzamide degradation. The loss of activity was attributed to starvation of the introduced bacteria because the micropollutant concentrations were low,

Fig. 3. Bioaugmentation with halophilic microorganisms. A bioaugmented open-air bioreactor in northern Oman (**Left**) just before and (**Right**) 1 year after seeding, as an example of hypersaline oil remediation technology. [Reprinted by permission from Springer Nature, (*31*).]

and metabolic competition occurred with more abundant assimilable organic carbon in the water (*44*, *45*).

Concluding remarks

The metabolic and stress-resistance traits that emerge in microorganisms in response to toxic compounds can be exploited for the bioremediation of spills of oil and chlorinated solvents, dissolution of valuable metals, and treating waste streams. However, designing sustainable bioremediation solutions, including those targeted at emerging micropollutants, is a major scientific challenge. The conceptual simplicity of bioaugmentation and attractiveness is deceptive, especially for single microbial strains (*44*–*46*). Microbiologists still have very little knowledge of the traits and conditions that need to be met to allow survival and population growth of nonnative microbes introduced into foreign ecosystems. The few studies that have measured the metabolic activities of inoculated bacterial strains in complex ecosystems have unveiled how divergent the biochemistry becomes in field conditions compared with the laboratory (*47*, *48*). Transposon library selection and sequencing have further shown just how many specific traits determine survival and proliferation in, for example, soil compared with the well-controlled conditions in the laboratory (*49*). Detailed experiments will be crucial for unraveling stress and resistance responses in inoculated strains and consortia and will be necessary to understand how productive metabolic traits can be deployed in order to functionally complement and restore contaminated ecosystems.

Genomic and allied technologies will permit better characterization of the prevailing resident microbial community in contaminated sites and inform community composition, xenometabolic potential, and adaptive capacity to adverse conditions. Meta-omic site diagnosis will provide inputs for advanced biogeochemical models (*50*, *51*). Such insights could be applied to diagnosing microbial communities for xenometabolic function at contaminated sites and for forecasting the success of specific measures, such as biostimulation or bioaugmentation, for accelerated bioremediation. Models could be expanded to address the potential roles of protozoan grazers and phage parasites that regulate microbial populations. For example, although phages can infect and eradicate populations of key detoxifier strains (*52*), they can also facilitate horizontal distribution of genes essential for bioremediation and as such promote degradation capacity.

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ACKNOWLEDGMENTS

We thank H. Stroo (Stroo Consulting) and C. Aziz (Ramboll) for providing photographs of bioaugmentation with OHRB, and H. Patzelt (Mazoon Environmental and Technological Services) for providing photographs of bioaugmentation with halophilic microorganisms. **Funding:** S.A., I.S.-A., and A.J.M.S. are supported by the Netherlands Ministry of Education, Culture and Science (project 024.002.002) and advanced ERC grant (project 323009). H.S. and S.A. were supported by a grant of BE-Basic-FES funds from the Dutch Ministry of Economic Affairs. H.S., J.R.v.d.M., and H.J.H. were supported by the European Commission (BACSIN, contract 211684; P4SB, contract 633962). **Competing interests:** The authors have no competing interests.

10.1126/science.aar3778